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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/561,307	12/19/2005	Adam Shapiro	100993-1P US	2778

44992 7590 07/08/2009

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EXAMINER
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ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
07/08/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/561,307	SHAPIRO, ADAM	
	Examiner	Art Unit	
	ANGELA BERTAGNA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☒ Claim(s) *1,2,5,6 and 14-16* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/30/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Preliminary Remark

1. Claims 1-16 are currently pending and will be examined on the merits.

Information Disclosure Statement

2. Applicant's submission of an Information Disclosure Statement on January 30, 2006 is acknowledged. A signed copy is enclosed. It is noted that the citation of non-patent literature reference AD has been corrected to reflect the fact that Maudru et al. authored the cited publication.

Drawings

3. The drawings filed on December 19, 2005 are acceptable.

Specification

4. The disclosure is objected to because of the following informalities: The specification contains boxes on pages 15-17 where it would appear that special characters were intended.

Appropriate correction is required.

Claim Objections

5. Claim 1 is objected to because of the following informalities: Replacing the terms "the template", "the primer", "the duplex", and "the hybrid duplex" with "the nucleic acid template",

"the nucleic acid primer", and "the primer-template hybrid duplex", respectively, is suggested to improve consistency within the claim.

Claim 2 is objected to because of the following informalities: Replacing the term "the template" with "the nucleic acid template is suggested to improve consistency with claim 1.

Claims 5 and 6 are objected to because of the following informalities: Replacing the term "the primer" with "the nucleic acid primer" is suggested to improve consistency with claim 1. Claim 5 also appears to be missing the word "the" before the words "nucleic acid template" in line 1. Claim 6 also recites "wherein is primer" in line 1, which is grammatically incorrect.

Claims 14 and 15 are objected to because of the following informalities: Replacing the terms "the template" and "the primer" with "the nucleic acid template" and "the nucleic acid primer", respectively, is suggested to improve consistency with claim 1.

Claim 16 is objected to because of the following informalities: Replacing the terms "the template", "the primer", "the duplex", and "the hybrid duplex" with "the nucleic acid template", "the nucleic acid primer", and "the primer-template hybrid duplex", respectively, is suggested to improve consistency within the claim.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8, 9, and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8 and 9 are indefinite, because they recite the limitation "the DNA polymerase" in line 1. There is insufficient antecedent basis for this limitation in the claims. There is sufficient antecedent basis for "the nucleic acid polymerase" (see claim 1).

Claim 14 is indefinite, because it recites the limitations "the first label" in line 1 and "the second label" in line 2. There is insufficient antecedent basis for these limitations in the claim. There is sufficient antecedent basis for "the label" (see claim 1).

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 7, 11, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Wittwer et al. (WO 97/46714 A1; cited on the IDS).

Claim 1 is drawn to a method for assaying polymerase activity that comprises incubating a labeled primer-template hybrid with a polymerase, subjecting the hybrid to denaturing conditions, and detecting a change in the signal from the label, thereby indicating the presence of polymerase activity. Claims 7, 11, and 15 further require use of a DNA polymerase, heat denaturation, and minimum lengths for the primer and template.

Wittwer teaches methods for monitoring hybridization during PCR.

Regarding claim 1, Wittwer teaches a method of detecting nucleic acid polymerase activity (see Example 8 on pages 45-46) comprising:

(a) providing a primer-template hybrid duplex comprising a nucleic acid template and a nucleic acid primer, wherein the primer, template or both the template and the primer comprise a label (see Example 8, page 45, where a Cy5-labeled primer-template complex is produced during the amplification)

(b) contacting the primer-template hybrid duplex with a nucleic acid polymerase (see Example 8, page 45, 2nd paragraph of the example, where Taq polymerase is used)

(c) subjecting the primer-template hybrid duplex to denaturing conditions (see Example 8, page 45, 2nd paragraph of the example, where incubation at 94°C is taught)

(d) detecting a signal from the label, wherein a change in the signal compared to a control is indicative of nucleic acid polymerase activity (see Example 8, page 45, 2nd paragraph of the example, where Cy5 fluorescence increases as a result of polymerase activity).

Regarding claim 7, Wittwer teaches that the polymerase is a DNA polymerase (see Example 8, page 45, 2nd paragraph of the Example, where Taq DNA polymerase is taught).

Regarding claim 11, Wittwer teaches that the denaturing conditions are achieved by application of heat (see Example 8, page 45, 2nd paragraph of the example, where incubation at 94°C is taught).

Regarding claim 15, Wittwer teaches that the primer is at least 6 nucleotides in length and that template is at least 10 nucleotides in length (see Example 8, page 45, 1st and 2nd paragraphs

of the example, where the primer is 20 nucleotides in length and the template is 110 nucleotides in length).

9. Claims 1-4, 7, 10, 11, 14, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Nazarenko et al. (US 5,866,336).

Claim 1 is drawn to a method for assaying polymerase activity that comprises incubating a labeled primer-template hybrid with a polymerase, subjecting the hybrid to denaturing conditions, and detecting a change in the signal from the label, thereby indicating the presence of polymerase activity. Claims 2-4 and 10 are drawn to the method of claim 1, further wherein the template is labeled with a FRET pair, specifically FAM/TAMRA. Claims 7, 11, and 15 are drawn to the method of claim 1 further wherein the nucleic acid polymerase is a DNA polymerase, the denaturing conditions are achieved via the application of heat, and the primer and template are at least 6 nucleotides and 10 nucleotides in length, respectively. Claim 14 is drawn to the method of claim 1, further wherein the primer is labeled at the 5' end, and the template nucleic acid is labeled at the 3' end.

Nazarenko teaches methods for detecting polymerase activity using fluorescently labeled primers (see abstract, Figures 1-3, column 2, lines 40-52, and columns 7-8 for a general description).

Regarding claim 1, Nazarenko teaches a method of detecting nucleic acid polymerase activity (see, for example, Example 6 at columns 36-43) that comprises:

(a) providing a primer-template hybrid duplex comprising a nucleic acid template and a nucleic acid primer, wherein the primer comprises a label (see column 37, line 60 - column 38, line 3 and column 38, lines 10-25; see also Figures 1-3 and 24)

(b) contacting the primer-template hybrid duplex with a nucleic acid polymerase (see column 38, lines 37-45; see also Figures 2-3)

(c) subjecting the primer-template hybrid duplex to denaturing conditions (see column 38, lines 37-45; see also Figures 2-3)

(d) detecting a signal from the label, wherein a change in the signal compared to a control is indicative of nucleic acid polymerase activity (column 38, lines 55-67; see also Figures 2-3).

Regarding claims 2-4, in the method of Nazarenko, the template is labeled with a first and second fluorescent label that constitute a FRET pair (see Figures 2-3, column 37, line 60 - column 38, line 3, and column 38, lines 10-25, for example, where after the first cycle of the PCR amplification method, the template is labeled with a first and second fluorescent label that constitute a FRET pair). Further regarding claims 3 and 4, it is noted that the designation of the first label and the second label is arbitrary, and therefore, in the method of Nazarenko, the 5' fluorescent label is the first label (*i.e.* the fluorescence donor), and the 3' fluorescent label is the second label (*i.e.* the fluorescence acceptor) or *vice versa*.

Regarding claim 7, the method of Nazarenko is conducted using a DNA polymerase (column 38, lines 37-45, for example).

Regarding claim 10, Nazarenko teaches that a suitable FRET pair for use in the method is FAM/TAMRA (see Table 1 at columns 17-18; see also column 18, lines 29-35).

Regarding claim 11, in the method of Nazarenko, the denaturing conditions are achieved via the application of heat (column 38, lines 37-45).

Regarding claim 14, Nazarenko teaches an embodiment of the method wherein the primer is labeled at the 5' end, and the template is labeled at the 3' end (see Figure 14a and column 35, line 54 – column 36, line 10, where the primer is fluorescently labeled at the 5' end, and the 3' end of the template is labeled with biotin).

Regarding claim 15, Nazarenko teaches that the primer is at least 6 nucleotides in length and that template is at least 10 nucleotides in length (see, for example, column 38, lines 10-36 and Figure 24).

10. Claims 1, 5, 7, 15, and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Yang et al. (Analytical Biochemistry (2002) 304: 110-116).

Claim 1 is drawn to a method for assaying polymerase activity that comprises incubating a labeled primer-template hybrid with a polymerase, subjecting the hybrid to denaturing conditions, and detecting a change in the signal from the label, thereby indicating the presence of polymerase activity. Claim 5 further limits the label to a radioisotope. Claims 7 and 15 further require use of a DNA polymerase and minimum lengths for the primer and template. Claim 16 is drawn to a method for assaying the effect of a test compound on polymerase activity that comprises incubating a labeled primer-template hybrid with a polymerase and a test compound, subjecting the hybrid to denaturing conditions, and detecting the signal from the label, wherein a change in the signal from the label compared to a control indicates that the test compound affects the activity of the polymerase.

Yang teaches methods for determining the effect of test inhibitor compounds on the activity of Pol-C type polymerase III from *Streptococcus pyogenes* (see abstract and page 110).

Regarding claim 1, Yang teaches a method of detecting nucleic acid polymerase activity comprising:

(a) providing a primer-template hybrid duplex comprising a nucleic acid template and a nucleic acid primer, wherein the primer, the template, or both the template and the primer comprise a label (see page 111, column 2 – page 112, column 1, where during practice of the method the primer in the primer-template hybrid duplex is labeled with a radioisotope)

(b) contacting the primer-template hybrid duplex with a nucleic acid polymerase (see page 111, column 2 - page 112, column 1)

(c) subjecting the primer-template hybrid duplex to denaturing conditions (see page 112, column 1, where the low pH resulting from the addition of the PVT-PEI SPA beads are denaturing conditions)

(d) detecting a signal from the label, wherein a change in the signal compared to a control is indicative of nucleic acid polymerase activity (see page 111, column 2 - page 112, column 1; see also pages 114-116 for further description of the method described above).

Regarding claim 5, in the method of Yang, the nucleic acid template is immobilized close to a scintillant molecule, and the primer is labeled with a radioisotope (see page 112, column 2).

Regarding claim 7, the method of Yang is conducted using a DNA polymerase (pages 111-112, for example).

Regarding claim 15, Yang teaches that the primer is at least 6 nucleotides in length and that template is at least 10 nucleotides in length (see Table 1 on page 113).

Regarding claim 16, Yang teaches a method of screening for compounds that modulate nucleic acid polymerase activity that comprises:

(a) providing a primer-template hybrid duplex comprising a nucleic acid template and a nucleic acid primer, wherein the primer, the template, or both the template and the primer comprise a label (see page 111, column 2 – page 112, column 1, where during practice of the method the primer in the primer-template hybrid duplex is labeled with a radioisotope)

(b) contacting the primer-template hybrid duplex with a nucleic acid polymerase and a test compound (page 111, column 2 – page 112, column 1)

(c) subjecting the primer-template hybrid duplex to denaturing conditions (see page 112, column 1, where the low pH resulting from the addition of the PVT-PEI SPA beads are denaturing conditions)

(d) detecting a signal from the label, wherein a change in the signal compared to a control indicates that the compound modulates nucleic acid polymerase activity (page 112, column 1; see also pages 114-116 for further description of the assay described above).

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yang et al. (Analytical Biochemistry (2002) 304: 110-116) in view of Malcolm et al. (US 6,211,338 B1).

Claim 6 is drawn to the method of claim 1, wherein the primer is immobilized close to a scintillant molecule, and the nucleic acid template is labeled with a radioisotope.

Yang teaches the methods of claims 1, 5, 7, 15, and 16, as discussed above.

Regarding claim 6, Yang teaches immobilizing a radiolabeled primer close to a scintillant molecule (see pages 111-112 and pages 114-116), but does not teach that the template nucleic acid is labeled with a radioisotope.

Malcolm teaches methods for conducting scintillation proximity assays using a primer-template hybrid duplex (see Example 7 at columns 30-31). Regarding claim 6, in the method of Malcolm, the primer and template nucleic acids are labeled with a radioisotope (see column 30, lines 10-27).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to label both the primer and template nucleic acids with a radioisotope when practicing the methods of Yang. An ordinary artisan would have recognized from the above teachings of Malcolm that the scintillation proximity assay disclosed by Yang could be conducted using a labeled primer, a labeled template, or a labeled template and a labeled primer. Therefore, an ordinary artisan would have been motivated to use any of these art-recognized equivalents when practicing the method of Yang with a reasonable expectation of success. As noted in MPEP 2144.06, it is *prima facie* obvious to substitute art-recognized equivalents known to be useful for the same purpose in the absence of unexpected results. Also, as noted in MPEP 2144.07, it is *prima facie* obvious to select a known material or method based on its suitability for the intended purpose in the absence of unexpected results. In this case, no evidence has been presented to suggest that the claimed method of conducting a scintillation proximity assay, wherein the

template nucleic acid is radiolabeled, is associated with unexpected results. Thus, the method of claim 6 is *prima facie* obvious over Yang in view of Malcolm in the absence of secondary considerations.

13. Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yang et al. (Analytical Biochemistry (2002) 304: 110-116) in view of Maki et al. (Journal of Biological Chemistry (1985) 260(24): 12987-12992).

Claims 8 and 9 are drawn to the method of claim 1, wherein the nucleic acid polymerase is a bacterial DnaE, specifically *E. coli* DnaE or *H. influenzae* DnaE.

Yang teaches the methods of claims 1, 5, 7, 15, and 16, as discussed above.

Yang does not teach that the nucleic acid polymerase is *E. coli* DnaE or *H. influenzae* DnaE as required by claims 8 and 9.

Maki discloses the isolation and purification of the *E. coli* DnaE polymerase (see abstract and pages 12987-12989). Maki also discloses suitable reaction conditions for using this polymerase (see page 12988).

It would have been *prima facie* obvious to conduct the method of Yang using any known DNA polymerase, such as the *E. coli* DnaE polymerase disclosed by Maki. An ordinary artisan would have recognized that the method of Yang was suitable for the analysis of any known DNA polymerase (*e.g.* the DNA polymerase disclosed by Maki), and therefore, would have been motivated to utilize the DNA polymerase disclosed by Maki when practicing the method of Yang in order to increase the number of useful applications of the method. As noted in MPEP 2144.07, it is *prima facie* obvious to utilize a known material or method based on its suitability

for the intended purpose in the absence of unexpected results. In this case, no evidence has been presented to suggest that the use of the claimed DNA polymerases is associated with unexpected results. Therefore, since the claimed *E. coli* DNA polymerase was known in the art, as evidenced by the teachings of Maki, and since the method of Yang was suitable for the analysis of any known DNA polymerase, the use of the claimed *E. coli* DNA polymerase in the methods of Yang is *prima facie* obvious in the absence of unexpected results.

14. Claims 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over **either** Wittwer et al. (WO 97/46714 A1; cited on the IDS) **or** Nazarenko et al. (US 5,866,336) in view of Kopf-Sill (US 6,303,343 B1).

Claims 12 and 13 are drawn to the method of claim 1, wherein the denaturing conditions are achieved by the addition of a chaotropic agent, specifically urea.

Wittwer teaches the methods of claims 1, 7, 11, and 15, as discussed above.

Nazarenko teaches the methods of claims 1-4, 7, 10, 11, 14, and 15, as discussed above.

Neither Wittwer nor Nazarenko teaches that the denaturing conditions are achieved by the addition of urea as required by claims 12 and 13.

Kopf-Sill teaches methods for conducting rapidly conducting PCR amplification reactions (see abstract and columns 2-3). Kopf-Sill teaches that the denaturation step of the PCR amplification methods may be performed via thermal denaturation or urea-induced denaturation (see abstract, column 3, lines 30-47, column 5, line 61 – column 6, line 2, and column 14, line 3 - column 15, line 8).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to substitute urea-induced denaturation for thermal denaturation when practicing the amplification methods taught by either Wittwer or Nazarenko. As noted above, Kopf-Sill taught that urea and heat were art-recognized equivalents known to be useful for achieving the same purpose, namelyDNA denaturation during PCR amplification. Therefore, in the absence of unexpected results, an ordinary artisan would have been motivated to substitute urea-induced denaturation for thermal denaturation when practicing the method of Wittwer or Nazarenko with a reasonable expectation of success. As noted in MPEP 2144.06, it is *prima facie* obvious to substitute art-recognized equivalents known to be useful for the same purpose in the absence of unexpected results. Also, as noted in MPEP 2144.07, it is *prima facie* obvious to select a known material or method based on its suitability for the intended purpose in the absence of unexpected results. In this case, since Kopf-Sill taught that either urea or heat could be used to denature DNA during PCR amplification (see above), an ordinary artisan would have been motivated to utilize urea-induced denaturation when practicing the methods disclosed by either Wittwer or Nazarenko with a reasonable expectation of success. It is also noted that no evidence has been presented to suggest that unexpected results are associated with a urea-induced denaturation step. Therefore, in the absence of secondary considerations, the methods of claims 12 and 13 are *prima facie* obvious over either Wittwer in view of Kopf-Sill **or** Nazarenko in view of Kopf-Sill.

Conclusion

15. No claims are currently allowable.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Furey et al. (Biochemistry (1998) 37: 2979-2990) teaches a method for monitoring polymerase activity that comprises the use of fluorescently labeled primers (see abstract and pages 2980-2983). Braslavsky et al. (Proceedings of the National Academy of Sciences, USA (2003) 100(7): 3960-3964) teaches a method for monitoring polymerase activity that comprises the use of fluorescently labeled primers (see abstract and pages 3961-3963).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANGELA BERTAGNA whose telephone number is (571)272-8291. The examiner can normally be reached on M-F, 9- 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cynthia B. Wilder/
Examiner, Art Unit 1637

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